REMARKS

Status of the Claims

Applicants have cancelled claims 29-46 and 48-60. Claims 47 and 61-82 are pending in the instant application. Claim 47 has been amended to more particularly point out and distinctly claim the subject matter which Applicants regard as their invention and to put the claim in condition for allowance. Support for the amended recitation of claim 47 is found on page 2, lines 6-8; page 6, line 20 to page 9, line 15; page 10, lines 13-15; page 12, lines 1-3; and page 15, line 2 of the Specification. Support for new claims 61, 62, 68, 76, 77, 80 and 81 is found on page 6, line 2 to page 7, line 15 of the Specification. Support for new claims 63 and 64 is found on page 10, line 13 to page 11, line 9 of the Specification. Support for new claim 65 is found on page 12, lines 4-8 of the Specification. Support for new claims 66, 78 and 82 is found on page 11, lines 20-28 of the Specification. Support for new claim 67 is found on page 12, line 22 to page 13, line 9 of the Specification. Additional support for new claims 68, 76 and 77 is found on page 3, lines 17-20 of the Specification. Additional support for new claim 68 is found on page 11, lines 10-14 of the Specification. Support for new claim 69 is found on page 2, lines 6-8 of the Specification. Support for new claims 70-74 is found on page 14, line 25 to page 15, line 6 of the Specification. Support for new claim 68 is found on page 2, lines 14-17 of the Specification. Additional support for new claim 77 is found on page 7, line 21 to page 9, line 15 of the Specification. Support for new claim 79 is found on page 17, line 2 to page 18, line 12 of the Specification. No new matter has been added. All of the claims under consideration, as amended, are presented as an APPENDIX attached hereto.

Summary of the Examiner's Office Action

The Office Action dated January 2, 1998 includes the following matters requiring response:

(1) Rejection of claims 29-34, 38-40, 43, 45, 48 and 50-54 under 35 USC § 102(e) as being anticipated by Greenberger;

(2) Rejection of claims 29-31, 33, 38, 48, 50 and 53-55 under 35 USC § 102(e) as being anticipated by Ohno *et al.*;

(3) Rejection of claims 41, 42 and 44 under 35 USC § 103(a) as being unpatentable over Greenberger in view of Engelhardt *et al.* and Kaufman;
(4) Rejection of claims 46, 47 and 49 under 35 USC § 103(a) as being unpatentable over Greenberger in view of Erzurum *et al.*;
(5) Rejection of claims 56-60 under 35 USC § 103(a) as being unpatentable over Greenberger in view of Erzurum *et al.*, Gage *et al.* and Naughton *et al.*;
(6) Rejection of claims 35-37 under 35 USC § 112, first paragraph;
(7) Objection to the Specification and rejection of claims 46 and 47 under 35 USC § 112, first paragraph;
(8) Rejection of claims 44, 48 and 50 under 35 USC § 112, second paragraph;

Each of the issues raised by the Examiner are discussed in order below. Applicants believe that the foregoing amendment and the following remarks respond completely to these issues. Applicants further believe that the pending claims as amended are in condition for allowance.

(1) Rejection of claims 29-34, 38-40, 43, 45, 48 and 50-54 under 35 USC § 102(e) as being anticipated by Greenberger.

Claims 29-34, 38-40, 43, 45, 48 and 50-54 stand rejected under 35 USC § 102(e) as being anticipated by Greenberger. Applicants have cancelled claims 29-34, 38-40, 43, 45, 48 and 50-54, therefore, the rejection is moot. Applicants traverse the rejection and submit that Greenberger in no way teaches or suggests Applicants' invention and, therefore, fails to anticipate Applicants' claimed invention.

Greenberger teaches a method of protecting normal cells against the toxic species of an anticancer agent or ionizing radiation by administering a polynucleotide encoding gamma glutamyl transpeptidase, superoxide dismutase or metallothionein. Delivery of a gene encoding MnSOD is exemplified in the application. The polynucleotide may be delivered by a replication defective adenovirus vector.

Applicants' claimed invention is directed to a method of treatment for a disease, wherein the disease is selected from the group consisting of atherosclerosis, cardiovascular disease, diabetes, retinopathy, cataract

formation, Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, 21 trisomy, and hypertension. The method of the invention comprises administering a replication defective, recombinant adenovirus comprising a DNA sequence which encodes a superoxide dismutase, that is capable of regulating superoxide dismutase activity, wherein the DNA sequence is under the control of a signal enabling expression in a target cell, to a patient suffering from such a disease.

Applicants submit respectfully that the Greenberger reference does not teach or suggest the invention as claimed. In particular, there is no hint or suggestion, much less the express teaching required for anticipation, of treatment of a disease as recited by the present claims. Indeed, Greenberger's teaching of prevention of damage in no way anticipates Applicants' invention. Based upon the instant amendment, Applicants respectfully submit that the rejection is moot and request that this rejection be withdrawn.

(2) Rejection of claims 29-31, 33, 38, 48, 50 and 53-55 under 35 USC § 102(e) as being anticipated by Ohno *et al.*

Claims 29-31, 33, 38, 48, 50 and 53-55 stand rejected under 35 USC § 102(e) as being anticipated by Ohno *et al.* Applicants have cancelled claims 29-31, 33, 38, 48, 50 and 53-55, therefore, the rejection is moot. Applicants traverse the rejection and submit that Ohno *et al.* in no way teach or suggest Applicants' invention and, therefore, fail to anticipate Applicants' claimed invention.

Ohno et al. teach methods of specifically irradiating tissues that contain a radiation responsive enhancer-promoter operatively linked to a structural gene encoding a polypeptide having the ability to inhibit the growth of a cell, particularly a tumor cell. The encoded polypeptide may be a free radical scavenger, particularly manganese superoxide dismutase and may be delivered to the tissues by an adenoviral vector. The methods of Ohno et al. require the use of radiation to induce expression of the therapeutic gene in the construct.

Applicants' claimed invention is directed to a method of treatment for a disease, wherein the disease is selected from the group consisting of atherosclerosis, cardiovascular disease, diabetes, retinopathy, cataract formation, Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, 21 trisomy, and hypertension, wherein the method comprises administering a replication defective, recombinant adenovirus

comprising a DNA sequence which encodes a superoxide dismutase, that is capable of regulating superoxide dismutase activity, wherein the DNA sequence is under the control of a signal enabling expression in a target cell, to a patient suffering from such a disease.

Applicants submit respectfully that the Ohno reference does not teach or suggest the invention as claimed. As noted above in connection with Greenberger, there is no hint or suggestion, much less the requisite express teaching, to treat a disease as recited in the claims. Based upon the instant amendment, Applicants respectfully submit that the claims are not anticipated by Ohno *et al.* and request that this rejection be reconsidered and withdrawn.

(3) Rejection of claims 41, 42 and 44 under 35 USC § 103(a) as being unpatentable over Greenberger in view of Engelhardt *et al.* and Kaufman.

Claims 41, 42 and 44 stand rejected under 35 USC § 103(a) as being unpatentable over Greenberger in view of Engelhardt *et al.* and Kaufman. Claims 41, 42 and 44 have been cancelled in the instant application, therefore, the rejection is moot. Applicants traverse the rejection and submit that Greenberger in view of Engelhardt *et al.* and Kaufman in no way teach or suggest Applicants' invention and, therefore, fail to render the claimed invention obvious to the skilled artisan.

Englehardt et al. teach second generation recombinant adenoviruses that contain a beta-galactosidase-expressing transgene and that also contains a temperature-sensitive mutation in the E2A gene of an E1-deleted recombinant virus.

Kaufman teaches vectors that may be used for expression in mammalian cells, however, Kaufman does not teach adenovirus vectors. Kaufman teaches constitutive promoters and teaches that the SV40 and adenovirus promoters are the best-characterized promoter systems (page 496, third paragraph). Kaufman teaches that most vectors for mammalian cells contain promoter elements from a variety of viral promoters, including the Rous sarcoma virus promoter (page 496, end of third paragraph). However, Kaufman teaches that the RSV-LTR is a transcriptional enhancer and that most expression vectors include a strong enhancer, frequently derived from SV40, RSV or CMV (page 497, first paragraph).

Applicants' claimed invention is directed to a method of treatment for a disease, as noted above. As discussed above, Greenberger does not teach Applicants' invention. Applicants submit respectfully that neither Englehardt *et al.* nor Kaufman supply the missing teaching of Greenberger. In particular, neither reference provides the suggestion to treat any of the recited diseases. Taken for what the references fairly teach, one of ordinary skill may at most be led to use the adenovirus vector of Englehardt *et al.* and/or the promoter of Kaufman to prevent free radical damage as disclosed by Greenberger. None of these references, taken individually or in any combination, suggest much less teach Applicants' invention as claimed.

Based upon the instant amendment and the novelty of Applicants' invention, Applicants respectfully submit that rejection is moot and request that this rejection be withdrawn.

(4) Rejection of claims 46, 47 and 49 under 35 USC § 103(a) as being unpatentable over Greenberger in view of Erzurum *et al.*

Claims 46, 47 and 49 stand rejected under 35 USC § 103(a) as being unpatentable over Greenberger in view of Erzurum *et al.* Applicants have cancelled claims 46 and 49. Claim 47 has been amended and is pending in the instant application. Applicants traverse the rejection and submit that Greenberger in view of Erzurum *et al.* in no way teach or suggest Applicants' invention and, therefore, fail to render the claimed invention obvious to the skilled artisan.

Erzurum et al. teach a replication deficient recombinant adenovirus containing the human catalase cDNA and the use of such an adenovirus to transfer the catalase cDNA to endothelial cells in order to confer intracellular anti-H_2O_2 protection.

As noted above, Applicants' claimed invention is directed to a method of treatment for a disease, wherein the disease is selected from the group consisting of atherosclerosis, cardiovascular disease, diabetes, retinopathy, cataract formation, Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, 21 trisomy, and hypertension, wherein the method comprises administering a replication defective, recombinant adenovirus comprising a DNA sequence which encodes a superoxide dismutase, that is capable of regulating superoxide dismutase activity, wherein

the DNA sequence is under the control of a signal enabling expression in a target cell, to a patient suffering from such a disease.

Erzurum *et al.* clearly do not teach Applicants' invention. Erzurum *et al.* teach the use an adenovirus encoding the human catalase gene to prevent oxidant-mediated injury. In addition, Erzurum *et al.* present no evidence to use a superoxide dismutase encoding adenovirus disclosed by Greenberger in a method to treat intracellular H_2O_2, much less the diseases as claimed by Applicants. *Erzurum et al.* certainly do not present any evidence to the skilled artisan that such a combination would work. The skilled artisan would not have reason to expect success without undue experimentation to cure the deficiencies of Greenberger with the teachings of Erzurum *et al.*

As discussed above, Greenberger does not teach Applicants' invention. Applicants submit respectfully that Erzurum *et al.* do not supply the missing teaching of Greenberger and therefore, do not render obvious the invention of the instant application. Neither of these references, taken individually or in any combination, suggest much less teach Applicants' invention.

In this case, nothing in the art cited by the Examiner teaches or suggests a method of treatment for a disease selected from the group consisting of atherosclerosis, cardiovascular disease, diabetes, retinopathy, cataract formation, Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, 21 trisomy, and hypertension, wherein the method comprises administering a replication defective, recombinant adenovirus comprising a DNA sequence which encodes a superoxide dismutase, that is capable of regulating superoxide dismutase activity, wherein the DNA sequence is under the control of a signal enabling expression in a target cell, to a patient suffering from such a disease. Therefore, the rejection must be based on improper hindsight derived from the benefit of Applicants' disclosure.

Based upon the instant amendment and the novelty of Applicants' invention, Applicants respectfully submit that the claims are non-obvious over Greenberger in view of Erzurum *et al.* and request that this rejection be reconsidered and withdrawn.

(5) Rejection of claims 56-60 under 35 USC § 103(a) as being unpatentable over Greenberger in view of Erzurum *et al.*, Gage *et al.* and Naughton *et al.*

Claims 56-60 stand rejected under 35 USC § 103(a) as being unpatentable over Greenberger in view of Erzurum *et al.*, Gage *et al.* and

Naughton *et al.* Applicants have cancelled claims 56-60, therefore, the rejection is moot. Applicants traverse the rejection and submit that Greenberger in view of Erzurum *et al.*, Gage *et al.* and Naughton *et al.* in no way teach or suggest Applicants' invention and, therefore, fail to render the claimed invention obvious to the skilled artisan.

Gage et al. teach methods of treating defects, disease or damage of cells in the central nervous system by grafting genetically modified donor cells into the central nervous system to produce a molecule that directly or indirectly provides a ameliorative effect. The grafts may contain a substrate that is capable of forming a solid plug to facilitate implantation.

Naughton et al. teach a three-dimensional cell culture system which may be used to culture cells and tissues in vitro for prolonged periods of time. These cultures may be transplanted or implanted in vivo or they may be used for cytotoxicity testing, compound screening or as bioreactors.

Applicants' claimed invention is directed to a method of treatment for a disease, as noted above. Gage *et al.* and Naughton *et al.* clearly do not teach Applicants' invention. As discussed above, neither Greenberger nor Erzurum *et al.* teaches Applicants' invention. Applicants submit respectfully that neither Gage *et al.* nor Naughton *et al.* supply the missing teaching of Greenberger and Erzurum *et al.* and therefore, do not render obvious the invention of the instant application. None of these references, taken individually or in any combination, suggest much less teach Applicants' invention. Based upon the instant amendment and the novelty of Applicants' invention, Applicants respectfully submit that this rejection is moot and request that this rejection be withdrawn.

(6) Rejection of claims 35-37 under 35 USC § 112, first paragraph.

The Examiner has rejected claims 35-37 under 35 USC § 112, first paragraph as allegedly containing subject matter which was not described in the Specification in such a way as to enable the skilled artisan to make and/or use the invention. In response, Applicants have cancelled claims 35-37. Based upon the instant amendment, Applicants respectfully submit that the rejection is moot and request that this rejection be withdrawn.

(7) Objection to the Specification and rejection of claims 46 and 47 under 35 USC § 112, first paragraph.

The Specification has been objected to for the alleged lack of an enabling disclosure for preventing diseases characterized by an excess of free radicals and claims 46 and 47 accordingly stand rejected under 35 USC § 112, first paragraph. Applicants have cancelled claim 46 and have amended claim 47 to obviate the Examiner's rejection and respectfully submit that the Specification is enabling for the invention as claimed. Based upon the instant amendment, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Applicants note that the Examiner has stated that the Specification is "enabling for a method of treating diseases characterized by an excess of free radicals" (page 10, last paragraph of the Office Action). Support added in proof of the enablement of Applicants' claimed invention is also found within Barkats *et al.*, 1996 (NeuroReport, 7:497-501; attached as EXHIBIT "A") and Barkats *et al.*, 1997 (Neuroscience, 78:703-713; attached as EXHIBIT "B") which are peer-reviewed articles[1] published subsequent to the filing of the instant application. Barkats *et al.*, 1996 demonstrate that adenoviral-mediated gene transfer of human CuZn superoxide dismutase (SOD) is an efficient means to produce CuZn SOD in neuronal cells. The authors demonstrate that the exogenous CuZn SOD enzyme is functional and that the resultant intracellular levels of CuZn SOD are sufficient to protect neurons from glutamate-induced cell death. Barkats *et al.*, 1997 demonstrate the use of intrastriatal grafts of embryonic mesencephalic rat neuronal cells that are infected *ex vivo* with a replication defective adenovirus encoding human CuZn SOD to treat Parkinson's disease in a rat model. The grafts exhibited sustained expression of the exogenous CuZn SOD for at least 5 weeks postgrafting and resulted in a more extensive functional recovery compared to the controls, as determined by rotational behavior. In addition, the inflammatory consequences of adenoviral gene transfer were minimal. Finally, the authors described a trend for improved graft survival after Ad-CuZnSOD infection which may be associated with the potential neuroprotective effect of intracellular overexpression of CuZn superoxide dismutase. Thus, EXHIBITS "A and B" demonstrate the effective transfer of

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[1] Barkats *et al.*, 1996 and Barkats *et al.*, 1997 are publications that include as co-authors inventors of this patent application. These articles represent a validation of the enabling disclosure of the instant application.

CuZn SOD by a replication defective recombinant adenovirus and EXHIBIT "B" further demonstrates the enablement of the method of treatment of Applicants' claimed invention. Thus, these EXHIBITS support the enablement of Applicants' disclosure within the Specification for a method to treat diseases using an adenovirus encoding a superoxide dismutase to those of skill in the art. The teachings of EXHIBITS "A and B" dispel any doubts that Applicants' invention provides a means to make and to use the invention as claimed.

(8) Rejection of claims 44, 48 and 50 under 35 USC § 112, second paragraph.

The Examiner has rejected claims 44, 48 and 50 under 35 USC § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants have cancelled claims 44, 48 and 50, therefore, the rejection is moot. In view of the foregoing amendments, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants request respectfully reconsideration and withdrawal of all rejections. Applicants further submit that the claims are in condition for allowance and an early notice to this effect is earnestly solicited.

If a telephone interview would be of assistance in advancing prosecution of this application, Applicants attorney invites the Examiner to contact him at the number provided below.

Dated: 4/2/98

Respectfully submitted,

Paul F. Fehlner

Rhône-Poulenc Rorer, Inc.
P.O. Box 5093, Mail Drop 3C43
Collegeville, PA 19426-0997
Telephone: (610) 454-3816
Facsimile: (610) 454-3808

Paul F. Fehlner, Ph.D.
Attorney for Applicants
Registration No. 35,135

APPENDIX

U.S. Patent Application Serial No. 08/765,026
"Adenovirus Including A Gene Coding For A Superoxide Dismutase"
RPR File No. ST94051-US
Claims Under Consideration

47. (Amended) A method of treatment for a disease, wherein the disease is selected from the group consisting of atherosclerosis, cardiovascular disease, diabetes, retinopathy, cataract formation, Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, 21 trisomy, and hypertension, wherein the method comprises administering a replication defective, recombinant adenovirus comprising a DNA sequence which encodes a superoxide dismutase, that is capable of regulating superoxide dismutase activity, wherein the DNA sequence is under the control of a signal enabling expression in a target cell, to a patient suffering from such a disease.

61. The method of treatment according to claim 47, wherein the DNA sequence is a cDNA sequence.

62. The method of treatment according to claim 61, wherein the cDNA sequence encodes human intracellular CuZn superoxide dismutase.

63. The method of treatment according to claim 47, wherein the signal enabling expression in a target cell is a viral promoter.

64. The method of treatment according to claim 63, wherein the promoter is selected from the group consisting of the E1A, MLP, CMV and RSV-LTR promoters.

65. The method of treatment according to claim 47, wherein the adenovirus lacks regions of its genome which are necessary for replication in a target cell.

66. The method of treatment according to claim 47, wherein the adenovirus comprises ITR sequences and an encapsidation sequence, and wherein the E1 gene and at least one of the E2, E4 or L1-L5 genes are non-functional.

67. The method of treatment according to claim 47, wherein the adenovirus is of a type selected from the group consisting of human Ad 2, human Ad 5, and canine CAV-2.

68. The method of treatment according to claim 62, wherein the cDNA sequence encodes human intracellular CuZn superoxide dismutase (SOD1) under the control of an RSV-LTR promoter.

69. The method of treatment according to claim 47, wherein the disease is retinopathy.

70. The method of treatment according to claim 47, wherein the disease is cataract formation.

71. The method of treatment according to claim 47, wherein the disease is Parkinson's disease.

72. The method of treatment according to claim 47, wherein the disease is Alzheimer's disease.

73. The method of treatment according to claim 47, wherein the disease is Huntington's disease.

74. The method of treatment according to claim 47, wherein the disease is amyotrophic lateral sclerosis.

75. The method of treatment according to claim 47, wherein the disease is hypertension.

76. The method of treatment according to claim 47, wherein the adenovirus comprises a DNA sequence which encodes intracellular CuZn superoxide dismutase (SOD1).

77. The method of treatment according to claim 47, wherein the adenovirus comprises a DNA sequence which encodes a human intracellular CuZn superoxide dismutase (SOD1).

78. The method of treatment according to claim 47, wherein the signal enabling expression in a target cell is a promoter permitting preponderant expression in the target cell.

79. The method of treatment according to claim 47, wherein the method comprises administering a cell infected with the replication defective, recombinant adenovirus to the patient.

80. The method of treatment of any one of claims 69-75, wherein the superoxide dismutase is intracellular CuZn superoxide dismutase (SOD1).

81. The method of treatment of any one of claims 69-75, wherein the superoxide dismutase is human intracellular CuZn superoxide dismutase (SOD1).

82. The method of treatment of any one of claims 69-75, wherein the adenovirus comprises ITR sequences and an encapsidation sequence, and wherein the E1 gene and at least one of the E2, E4 or L1-L5 genes are non-functional.